REMARKS

Claims 7 and 14 have been amended as set forth in the above complete listing of the claims. Claim 10 has been cancelled. Upon entry, claims 7, 8, 11-14, 22, and 23 will be pending.

Claim 7 has been amended to incorporate the elements of previously pending claim 10. Claim 14 has been amended to more clearly define the subject matter regarded as the invention. The amendments are supported throughout the specification and in the claims as originally filed and, therefore, do not add new matter.

Objection to the Specification

The amendment filed August 4, 2003, including the substitute sequence listing having SEQ ID NOS:115-118, is objected to under 35 U.S.C. § 132 as introducing new matter into the specification. In particular, it is alleged that the primers set forth as SEQ ID NOS: 115-118 are not supported by the specification as originally filed.

Applicants respectfully traverse the objection and submit that one of skill in the art, viewing the current disclosure at the time of filing, would have been able to identify unmethylated and methylated sequence primers given the short nucleic acid sequence of ppENK provided in SEQ ID NO:8 or in the public databases (e.g., GenBank Accession No. X00187), including those primers set forth as SEQ ID NOS: 115-118. It is further stated in the Office action that although SEQ ID NOS: 115-118 were derived from SEQ ID NO: 8, an alignment and search of SEQ ID NO:8 revealed little sequence homology compared to the primer sequences set forth as SEQ ID NOS: 115-118. Applicants point out, however, that methods of detecting aberrant methylation of a gene are described in the specification which include processing steps, prior to PCR amplification, that result in predictable alterations in nucleic acid structure. In particular, the specification exemplifies using methylation-specific PCR (MSP), including bisulfite modification and bisulfite-modified genomic sequencing. Chemical modification of a nucleic acid by bisulfite treatment includes modification of

unmethylated cytosine to uracil, while methylated residues (5-methylcytosine) are resistant to such modification. Bisulfite modified nucleic acids are then amplified and sequenced, providing information within the amplified region of the methylation status of the nucleic acid (see, e.g., Example 4; see also, Ueki, et al., Cancer Res., 60:1835-1839, 2000, which is cited in the current specification, and attached hereto as Exhibit A). For example, Exhibit B, which is attached hereto, provides for illustrative purposes a listing of Genebank Accession No. X00187 as well as sequences representing unmethylated and methylated sequences of the ppENK 5' flanking region, processed as described in the specification, marked to illustrate binding regions for the primer sequences set forth in the claims. As such, one skilled in the art would not expect primers used for PCR analysis of a nucleic acid following bisulfite treatment (e.g., MSP analysis) to be limited only to primer sequences having exact homology with the sequences not subjected to bisulfite treatment.

Thus, for the reasons set forth above, it is submitted that the sequences set forth as SEQ ID NOS: 115-118 are fully supported in the specification as originally filed. Accordingly, withdrawal of the objection under 35 U.S.C. § 132 is respectfully requested.

Rejection Under 35 U.S.C. § 112

The rejection of claims 7-8, 12-14, 22 and 23 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed.

It is acknowledged in the Office Action that the specification is enabling for a method for detecting a cellular proliferative disorder associated with pancreatic cancer or colorectal cancer in a subject by identifying aberrant methylation regions of the gene or regulatory region, wherein the aberrant methylation comprises hypermethylation and is identified as being different when compared to the same region of the gene or associated regulatory region in a subject not having said cellular proliferative disorder. It is alleged, however, that the specification does not reasonably provide enablement for a method for detecting a cellular proliferative disorder in a subject by identifying any aberrant methylation (e.g.,

hypermethylation and hypomethylation) or in any tissue type or nucleic acid containing specimen. As such, it is alleged that undue experimentation would have been required for one skilled in the art to practice the claimed methods.

Although Applicants respectfully traverse the rejection, the claims have been amended in order to advance the prosecution of the current application. In particular, claim 7 has been amended to incorporate the elements of claim 10, as suggested by the Examiner. As such, claim 7, as currently presented, is more particularly drawn to a method for detecting in a subject a cellular proliferative disorder associated with pancreatic cancer or colorectal cancer including identifying aberrant methylation of regions of the gene or regulatory region, wherein aberrant methylation comprises hypermethylation when compared to the same regions of the gene or associated regulatory regions in a subject not having the cellular proliferative disorder. Further, claim 14 has been amended to recite those nucleic acid specimens most directly related to pancreatic cancer or colorectal cancer.

As such, for the reasons set forth above, Applicants submit that the rejection is rendered moot in light of the currently amended claims. Accordingly, removal of the rejection of claims 7-8, 12-14, 22 and 23 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

The objection to the specification and corresponding rejection of claim 22 under 35 U.S.C. § 112, first paragraph, as allegedly being drawn to subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention at the time of filing, is respectfully traversed.

It is alleged in the Office action that the primer sequences recited as SEQ ID NOS:115-118 were not specifically recited and, therefore, not supported in the specification as originally filed. Applicants respectfully submit, however, that it is not necessary that the specification individually list each and every primer nucleic acid sequence suitable for use in

the inventive methods, because, in light of the guidance provided in the specification, design and testing of such sequences would have been within the ordinary skill of those in the art.

As set forth above, Applicants submit that one of skill in the art, viewing the current disclosure at the time of filing, would have been able to design and test unmethylated and methylated sequence primers given the short nucleic acid sequence of ppENK provided in SEQ ID NO:8 or in the public databases (e.g., GenBank Accession No. X00187), including those primers set forth as SEQ ID NOS: 115-118. Furthermore, regarding the lack of homology between SEQ ID NO:8 compared to the primer sequences set forth as SEQ ID NOS: 115-118, Applicants respectfully point out that methods of detecting aberrant methylation of a gene set forth in the specification include processing steps, prior to PCR amplification, that result in alterations in nucleic acid structure. The specification exemplifies modification of nucleic acids including bisulfite modification and bisulfite-modified genomic sequencing for methylation-specific PCR (MSP) (see, e.g., Example 4). Bisulfite treatment of nucleic acids results in modification of unmethylated cytosine to uracil, while methylated residues (5-methylcytosine) are resistant to such modification. Modified nucleic acids are then amplified and sequenced, providing information within the amplified region of the methylation status of the nucleic acid (see also, e.g., Ueki, et al., Cancer Res., 60:1835-1839, 2000; Exhibit A).

Therefore, for the reasons set forth above, Applicants respectfully submit that one skilled in the art, viewing the specification, would reasonable have known that Applicants were in possession of the claimed invention at the time of filing. Accordingly, removal of the rejection of claim 22 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 07-1896.

Respectfully submitted,

Date: 6/15/05

Lisa A. Haile, J.D., Ph.D.
Registration No.: 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO CUSTOMER NO. 28213

Attachment: Exhibits A & B